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ARTICLE

Investigations into implantation failure in oocyte-donation recipients

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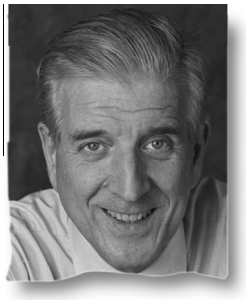

Pedro N. Barri Ragué graduated from the Faculty of Medicine in Barcelona in 1971 and trained in obstetrics and gynaecology in Barcelona, France and England. He received his doctorate in 1993 and in December 2003, he was nominated a Corresponding Academician of the Reial Acadèmia of Medicine of Catalonia. At present, Pedro is the Director of the Department of Obstetrics, Gynaecology and Reproduction of the Institut Universitari Dexeus of the Universitat Autònoma de Barcelona, where he is the Director of the Chair of Investigation in Obstetrics and Gynaecology since January 2011.

Abstract In recent decades, the Western world has been experiencing a societal trend to prioritize the professional careers of women who postpone motherhood to about 40 years of age, when, unfortunately, natural reproductive potential declines. This is the reason why these women increasingly find it necessary to resort to oocyte donation to have a child. Thanks to the young age of the donors, the efficacy of oocyte donation is the highest of all assisted reproduction treatments and pregnancy rates achieved with this technique exceed 50%. Moreover, the large registries from ESHRE and ASRM show live birth rates close to this figure. However, there are patients who experience repeated failures in several oocyte-donation cycles, and so far oocyte-donation repeated implantation failure has not been clearly defined. This study analysed the results obtained from 2531 oocyte-donation cycles carried out in 1990 patients and defines oocyte-donation repeated implantation failure as failure to implant with more than two embryo transfers and more than four high-grade embryos transferred. This study observed this condition in 140 oocyte recipients (7%). Also, oocyte cohort size, uterine factors and systemic thrombophilias as important aetiological factors were identified were to offer new therapeutic strategies to patients.

KEYWORDS: implantation failure, infertility, IVF, oocyte donation

Introduction

In the last three decades, the efficacy of assisted reproduction treatments has made great strides forwards, sometimes even exceeding the natural reproductive ability of the human species. Nevertheless, there is a group of infertile couples who repeatedly fail successive attempts at IVF, thereby suffering a personal tragedy (Penzias, 2012; Simon and Laufer, 2012). It seems that the explanation of these repeated failures has to be sought in the low quality of the embryos that these couples produce rather than in problems associated with the patients themselves (Das

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and Holzer, 2012; Patrizio et al., 2006). A number of publications have tried to establish a link between the total number of oocytes and embryos available for the treatment and the live birth rates achieved (Garrido et al., 2011; Sunkara et al., 2011).

The societal trend towards delaying motherhood that is to be found in the developed countries has meant that many women seek to become pregnant for the first time at about 40 years of age, at which point their natural reproductive potential has declined. For this reason, such couples increasingly find it necessary to resort to oocyte donation in order to have a child. The efficacy of oocyte donation is the highest of all assisted reproduction treatments, because the donors are young, usually under 35 and have no history of disease. However, there are patients who fail even after several egg donation cycles. Looking at the overall results obtained with this technique that have been published in different registers, in 2009, with more than 29,892 egg donation cycles carried out in the world, 14,647 live births were achieved, which means that 51% of cycles failed to produce a live birth (CDC-ARSM-SART, 2011; Ferraretti et al., 2012; Prados et al., 2011).

There are differing hypotheses that set out to explain the reasons why patients who receive oocytes fail repeatedly (oocyte-donation repeated implantation failures; OD-RIF). Some authors have shown that it is not possible to identify the factors that are potentially associated with this situation (Bodri et al., 2007). There is no consensus on the requirements that each of these cases must meet to be classified as OD-RIF (i.e. there is no definition of this condition). For this reason, the purpose of this study was to analyse this study centre's data and try to establish its own definition of OD-RIF is while also identifying various factors that may be responsible for this repeated failure and evaluating the results that can be obtained with several therapeutic strategies.

Materials and methods

This is a retrospective cohort study conducted with the data obtained from 2531 oocyte-donation cycles carried out in the Department of Obstetrics, Gynecology and Reproduction of the Hospital Universitario Quirón Dexeus. The analysis of these data was approved by the institutional review board (reference no. CIOG 16052012/03, approved 16 May 2012).

This study performed a global analysis of the data from the patients who had more than one embryo transfer originating from an oocyte-donation cycle, with the intention of finding out the number of embryo transfers and of high-grade embryos transferred at which there was a significant fall in the clinical pregnancy rate (with positive heart beat at 7-week ultrasound scan) per new oocyte-donation cycle. Embryo quality was assessed taking into account the number of blastomeres, their size and shape, the percentage of fragmentation and multinucleation. Embryos graded with a score $\geq$6 on a scale of 1–10 were considered embryos available to be transferred or frozen. Embryos graded with a score $\geq$8 were considered good-quality embryos (Clua et al., 2010).

In the group of 140 patients with clinical criteria for OD-RIF, this study did an in-depth study of the influence of the male factor with sperm DNA fragmentation and sperm fluorescence in-situ hybridization (FISH) analysis. Sperm DNA fragmentation index was measured by the sperm chromatin dispersion test using the Halosperm kit (normal $<$30%; (Halotech DNA, Madrid, Spain). Sperm FISH analysis was performed using commercial hybridization probes (Aneuvysion Multicolor DNA Probe Kit, Abbott Molecular, Illinois, USA) for chromosomes 13, 18, 21, X and Y. In women, uterine anomalies (hysteroscopy) and systemic pathology (congenital or acquired thrombophilia) were investigated.

Selection of donors and recipients

The donors were selected in accordance with the current applicable legal regulations in Spain and all donors met the required inclusion criteria with regard to age 18–35 years, normal karyotype, negative serological screening, and no hereditary diseases with relevant background or severe psychiatric diseases, as assessed by questionnaire and normal psychological tests (The Wender Utah Rating Scale, June 1993; Ramos-Quiroga JA et al., 2009). In the evaluated cycles, the study centre's followed its normal policy of assigning a single recipient for each donor. Oocyte donors underwent only one cycle of oocyte donation.

The recipients in this study centre must be aged no more than 50 years, have a receptive uterus capable of implanting embryos with a normal uterine cavity on ultrasound scan ruling out uterine pathology and be in a good state of physical and mental health that does not counterindicate a pregnancy. The vast majority of recipients are nulliparous, and only 142 (7.1%) in this study had previously been pregnant.

IVF and fresh embryo transfer

Ovarian stimulation of the donors was carried out as previously described (Martinez et al., 2008) with the use of leuprolide acetate 3.75 mg for pituitary desensitization (Procrin; Abbott Laboratories, Madrid, Spain) and human menopausal gonadotrophin (HMG Lepori; Farma Lepori, Barcelona, Spain). When at least three follicles measuring $>$20 mm were observed, a bolus of 5000 IU human chorionic gonadotrophin (HCG Lepori; Farma Lepori) or 250 μg recombinant HCG (Ovitrelle; Merck Serono, Madrid, Spain) or 0.2 mg triptoreline (Decapeptyl; Ipsen Farma, Barcelona, Spain) was administered and transvaginal oocyte retrieval was performed 36 h later under sedation with propofol. Gonadotrophin-releasing hormone (GnRH) antagonists were also used in other cases after a previous cycle of oral contraceptives at a daily dose of 0.25 mg Cetrorelix (Merck Serono) or 0.25 mg ganirelix (Orgalutran; MSD, Madrid, Spain) combined with 150-200 IU daily recombinant FSH (Gonal; Merck Serono; or Puregon; MSD, Madrid, Spain).

Recipients with normal ovarian function were down-regulated with a long-acting GnRH agonist (Decapeptyl) administered between days 20–22 of the previous cycle. Endometrial preparation included 2 mg oestradiol valerate every 8 h (Progynova; Bayer, Barcelona, Spain) and 200 mg vaginal micronized progesterone every 8 h (Utrogestan; Seid, Barcelona, Spain) from the day previous to the oocyte retrieval. Women without ovarian activity received the same protocol but without GnRH administration (Martinez

et al., 2006). Intracytoplasmic sperm injection was not universally used and was applied when low sperm quality made it advisable (1356/2531, 53.6%).

Embryo freezing and frozen—thawed embryo transfers

In more than half of the oocyte-donation cycles, it proved possible to freeze surplus embryos. The freezing took place on day 3 post oocyte retrieval following a conventional slow protocol for embryo cryopreservation (Veiga et al., 1987). Occasionally, a prolonged culture up to day 6 was followed and the blastocysts that were obtained were frozen.

The frozen embryos were always transferred under an artificial cycle substituted with the same regime of oestradiol valerate administered orally and micronized vaginal progesterone.

Statistical analysis

The quantitative variables were compared using the Student's t-test or the Mann—Whitney test, depending on the necessary assumptions. Categorical variables were compared using Fisher's exact test or the chi-squared test. All of the test were bilateral, with a significance level of 5%.

The criteria for OD-RIF were identified from Pareto charts of clinical pregnancy rates by total number of embryos transferred and number of high-grade embryos in fresh and frozen cycles and their impact on the cumulative clinical pregnancy rate. In order to analyse the relationship between the retrieved oocytes and the viable embryos and between the retrieved oocytes and the live birth rate, separate generalized additive models were estimated.

Results

Overall results

Forty-five percent of the donors received a short protocol of GnRH antagonist and gonadotrophins, while 55% had received a long protocol of GnRH agonists and gonadotrophins.

There were no significant differences between the two groups in mean consumption of gonadotrophins (2075 ± 226 IU, the plasma oestradiol concentration reached on the day of the ovulatory discharge (2144.3 ± 1031.6 pg/ml) or in the mean number of oocytes retrieved (11.6 ± 5.6).The mean age of the recipients included in this study was 41.2 ± 5.2 years, their mean body mass index was 22.4 ± 2.4 kg/m^2 and 21% of them smoked. The donors' mean age was 26.8 ± 4.4 years, their mean body mass index was 22.5 ± 1.7 kg/m^2 and 45% of them regularly smoked more than 10 cigarettes a day. There were no differences in age, body mass index or smoking status between pregnant and non-pregnant patients.

All embryo transfers were performed on day 2 after the oocytes were obtained and a mean number of 2.0 ± 1.1 embryos were transferred.

There were 14 cases of severe ovarian hyperstimulation observed in the group of donors stimulated under agonists (3.1%), of whom six required hospitalization, and after the transfer of embryos from these donors, seven recipients became pregnant. No ovarian hyperstimulation syndrome was observed among the donors who had been treated with antagonists and who received an ovulatory discharge with agonists.

Out of the 2531 egg-donation cycles carried out in 1990 patients that were evaluated, 1316 clinical pregnancies were obtained (52.0% pregnancies/cycle); of these 208 were a miscarriage in the first trimester (15.8% miscarriage rate) and 1108 (84.2%) ended as live births. Of the live births, 232 (20.9%) were twin and five (0.5%) were triplets. Recipient's clinical pregnancy rates according to the GnRH analogue used in the donor (agonist or antagonist) were similar (53.4% versus 51.6%).

Of the 140 patients with OD-RIF, 54 had undergone an additional third cycle and nine became pregnant (16.7%). This percentage was significantly lower than the rate that was normally obtained in the first two oocyte-donation attempts (49.8% clinical pregnancy rate per attempt; $P < 0.05$).

Definition of OD-RIF

According to this study centre's data, the expectations of pregnancy with a new attempt at oocyte donation are noticeably lower when a recipient has already had more than two embryo transfers with a total of more than four fresh or frozen—thawed high-grade embryos transferred. This is what this work has taken as its definition of OD-RIF. This condition was observed in 140 recipients (7.0%), and there were 585 failures (29.4%) that did not fulfil this definition of OD-RIF.

Number of oocytes retrieved and live birth rate

This study revealed a positive relationship between the total number of metaphase-II oocytes retrieved and the pregnancy and live birth rates, up to 15 oocytes. However, this association disappeared if more oocytes were retrieved and the live birth rate tended to plateau. (Figures 1 and 2). If more than 15 oocytes were retrieved from the donor, clinical pregnancy (107/353, 30.3% versus 1178/2173, 54.2%, $P < 0.05$) and live birth rates (92/353, 26.1% versus 1045/2173, 48.1%, $P < 0.05$) in the recipients tended to fall significantly compared with the results obtained in recipients when less than 15 oocytes were retrieved in from donor.

This study also analysed the cumulative data obtained for each oocyte, accumulating the results obtained in fresh cycles and those achieved with the later frozen—thawed embryo transfers. Following the concept of oocyte to baby rate (Patrizio and Sakkas, 2009), this study found a negative relationship between the number of available oocytes and/or embryos and the final cumulative live birth rate (Table 1). Also, the embryo per oocyte rate had a decreasingly positive relationship with the total number of oocytes retrieved (Figure 3) and this effect was not related to the donor's age (46.7% for donors $\leq$25 years, 49.2% for 26—30 years, 49.3% for 31—35 years).

Level of endometrial preparation

This study could not differentiate the mean plasma concentrations of oestradiol and progesterone measured on the day prior to the embryo transfer between the group of patients

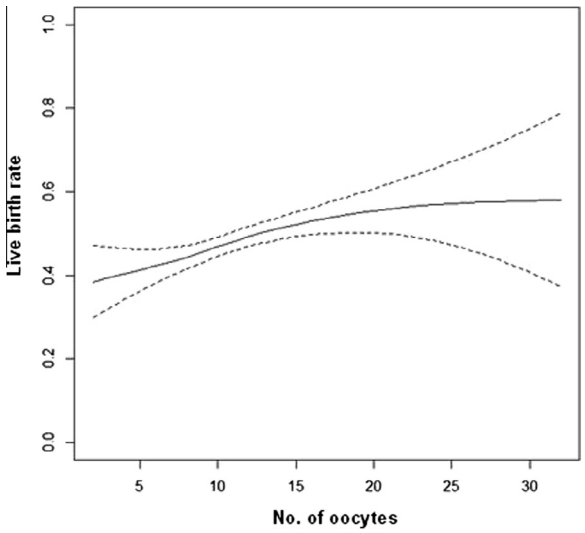

Figure 1 The relationship between the number of metaphase-II oocytes retrieved and the live birth rate. The solid line indicates the mean rate and the dotted lines indicate 95% confidence interval.

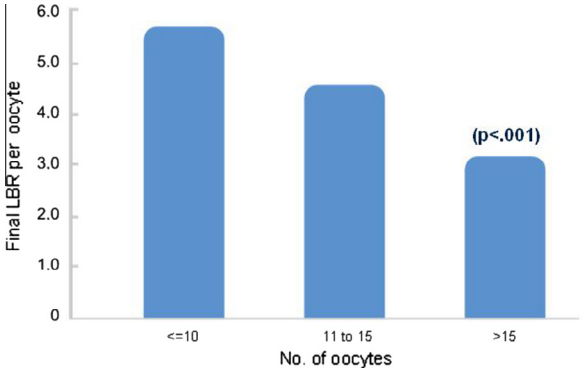

Figure 2 The relationship between the number of metaphase-II oocytes retrieved and the live birth rate (LBR) per oocyte.

who became pregnant (oestradiol 273.3 ± 122.5 pg/ml and progesterone 10.3 ± 4.5 ng/ml) and those who did not (oestradiol 297.5 ± 128.8 pg/ml and progesterone 11.6 ± 6.2 ng/ml).

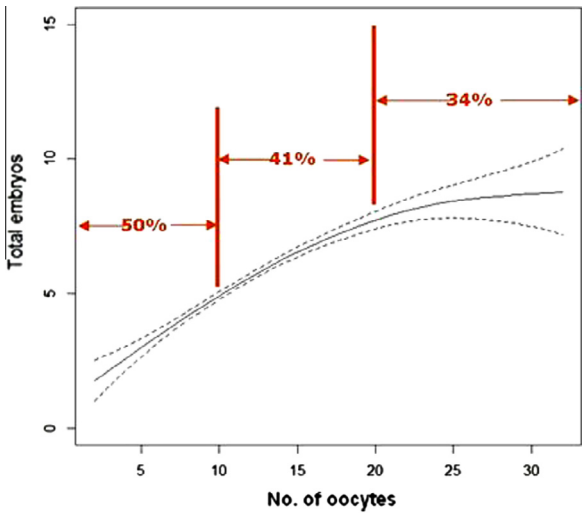

Figure 3 Numbers of embryos formed in relation to the total number of metaphase-II oocytes retrieved. The solid line indicates mean number of embryos and the dotted lines indicate 95% confidence interval. Percentages represent the embryo per oocyte rate ($P < 0.05$ for 50% for <10 oocytes versus 34% for >20 oocytes).

Endometrial thickness on the day of the embryo transfer showed no significant difference between the group of patients who achieved a pregnancy and those who did not (10.8 ± 2.69 mm versus 10.2 ± 2.17 mm).

Andrological data

The age of the men included in this study showed no influence on pregnancy (42.9 ± 6.2 years) or non-pregnancy (43.4 ± 5.9 years) or on miscarriage (43.1 ± 5.9 years) or live birth (42.9 ± 7.1 years). Among this OD-RIF group, there were 64 patients with abnormal male factor (48%). After confirming that their karyotype was normal, they were studied and showed an altered fragmentation of sperm DNA in 22 patients (34.4%) of the cases. No significant differences were found in the clinical pregnancy rates achieved in the patients with pathological DNA fragmentation compared with those with normal values (14/22, 63.6% versus 17/42, 40.5%). Fourteen patients (21.9%) showed a pathological sperm FISH result. No difference was found in the clinical pregnancy rates in patients who had a pathological sperm

Table 1 Live birth rates according to the number of oocytes retrieved and embryos available.

No. of oocytes retrieved	*Cycles* (n)	*Oocytes* (n)	*Embryos available* (n)	*Embryos transferred (fresh + frozen–thawed)* (n)	*Live births* (n)	*LBR per oocyte* (%)	*Oocytes for a live birth* (n)	*LBR per embryo available* (%)	*Embryos for a live birth* (n)	*Implantation rate* (%)
≤5	70	302	186	149	29	9.60	10.41	15.59	6.41	30.2
6–10	1020	8709	4908	2866	435	4.99	20.02	8.86	11.28	26.13
11–15	1083	13725	6718	3288	570	4.15	24.08	8.48	11.79	28.6
16–20	292	5114	2125	955	151	2.95	33.87	7.11	14.07	29.4
21+	61	1454	513	223	36	2.48	40.39	7.02	14.25	30.4
Total	2526	29,304	14,450	7481	1221	4.17	24.00	8.45	11.83	28.25

LBR = live birth rate.

FISH result compared with those with a normal result (7/14, 50% versus 25/50, 50%). Fourteen of these 64 patients with abnormal male factor underwent a new attempt with preimplantation genetic screening (PGS) (Table 2) .

Uterine factors

Hysteroscopic study was performed in the 140 patients who had failed at least twice in an oocyte-donation cycle. There were pathological findings in the uterine cavity in 60 (42.9%) of these patients, with polyps (20), endometritis (18), myomas (nine), adhesions (12), adenomyosis (four) and malformations (eight) being the most common findings. Of these patients, 38 underwent a new attempt after treatment for the uterine pathology observed, and 16 (42.1%) became pregnant. On the other hand, of the 53 patients with a normal hysteroscopy who underwent a further attempt, only 15 (28.3%) became pregnant ($P < 0.05$).

Systemic factors

In the 131 patients of the 140 who had failed twice in oocyte donation, this study was able to screen for congenital or acquired thrombophilia, including tests for homocysteine, resistance to the activated protein C, lupus anticoagulant, anticardiolipin antibodies and of the factor II and factor V Leiden mutations. In 21 patients (16%), this study showed abnormal results.

Discussion

Oocyte-donation programmes offer the highest pregnancy rates of the various assisted reproduction treatments. However, there is a group of patients who fail repeatedly in successive oocyte-donation cycles. In the light of this study centre's experience, this study considers that a patient presents as an OD-RIF when she has received more than two transfers with more than four high-quality embryos transferred in total. Although some authors have suggested that five embryos was the number at which these patients should be studied in greater depth (Garrido et al., 2012), it is useful to include embryo quality and the number of embryo transfers performed. For this reason, it is essential to study these patients more deeply when they meet OD-RIF criteria before starting a new attempt at treatment.

Table 2 Preimplantation genetic screening in a subset of oocyte-donation recurrent implantation failure patients.

Etiology and PGS cycle outcome	
Cycles	28
Andrological factors (abnormal FISH, meiosis, or karyotype)	14 patients
Other indications (previous implantation failures, patient's wish)	14 patients
Metaphase-II oocytes/cycle	13 ± 2.4
Embryos biopsied	7.8 ± 1.3
Abnormal embryos	150/225 (66.7)
Embryo transfers	24
No. of embryos transferred	1.7 ± 0.8
Clinical pregnancies	14/28 (50.0)
Clinical pregnancies/embryo transfer	14/24 (58.3)

Values are *n*, mean ± SD or *n*/total (%).
FISH = fluorescent in-situ hybridization.

There were no significant differences between the ages of donors and recipients in terms of whether or not a clinical pregnancy was achieved. However, this study did note a significant trend towards a greater miscarriage rate when the donors were aged over 26 years than when they were younger (18.9% versus 12.5%, $P < 0.001$). As in other studies (Bodri et al., 2007), this sample showed no association between the infertility factor and the final outcome of the cycle.

One important aspect to be borne in mind is the influence of the ovarian stimulation and the response of the donors (Faddy et al., 2011). The current analysis included all kind of oocytes retrieved. Even with the use of non-aggressive stimulation protocols that combine GnRH antagonists, modest doses of gonadotrophins and an ovulatory discharge with GnRH agonists in order to obtain a moderate response, it was found that if more than 15 oocytes were retrieved in the donor, the clinical pregnancy and live birth rates in the recipients decreased compared with cycles with <15 oocytes retrieved from the donor. This finding agrees with figures published in a group of donors from whom at least two live births had been obtained and in whom the same negative correlation was found (Ryan Martin et al., 2010). These results would explain the worse oocyte quality which, together with inadequate endometrial preparation, have been held responsible for the low live birth rates that are achieved in the IVF cycles in which there is a high response. Moreover, the availability of a high number of oocytes has been presented as an advantage since they can also produce a large number of oocytes or embryos for freezing, thus increasing the chances of achieving a pregnancy (Rienzi et al., 2012). This study centre's experience, in which all oocytes and embryos obtained have been used, is in line with that of Patrizio and Sakkas (2009) in that an analysis of the concept of oocyte or embryo to baby rate shows that combining fresh and frozen embryo transfers originating from the initial pool of available oocytes showed worse results on increasing the size of the initial cohort of oocytes. In the current study, it is believed that the sample analysed is large enough to draw this conclusion; also that, although some more pregnancies will be obtained from the transfer of the remaining frozen embryos, the trend in the different categories will not change.

There is still a need for a proper andrological study of men who present seminal pathology, even though all male partners were karyotyped and neither the age of the male nor sperm DNA fragmentation proved useful in identifying patients with the best prognosis. Nevertheless, these two tests did not differentiate adequately between the cycles that ended in a pregnancy and those that did not. PGS was beneficial in treating patients with altered sperm FISH who had failed in previous oocyte-donation cycles (Table 2).

The uterine factor must be taken into account in cases of OD-RIF (Reis Soares et al., 2003) and special attention must

be paid to the cases of patients with previous pelvic irradiation and very thin endometrium that is refractory to most treatments. This study's hysteroscopic findings has shown that that nearly half of these patients have some kind of intracavitary pathology (Julve Simon et al., 2012). It is also important to bear in mind that many of the anomalies detected can be treated easily (Shariff and Ghunaim, 2010), although controversy surrounds the possible benefit of the therapy that is applied; there are authors who claim that the treatment does not improve the later outcome (Johnston-MacAnanny et al., 2010) and others who use a meta-analysis to claim that, by means of a hypothetical endometrial irritative effect, even a normal hysteroscopy significantly improves the subsequent pregnancy rate (El-Thouky et al., 2008). The new possibilities for studying the endometrial gene pattern will certainly open up new diagnostic and therapeutic possibilities for the management of these patients.

One strategy for the clinical management of patients with OD-RIF is the application of extended culture techniques for subsequent blastocyst transfer. On one hand, this technique will make it possible to know whether a couple has a normal rate of blastocyst formation, while on the other hand, it is probable that the final pregnancy rate will increase to reach levels higher than those normally found in IVF with the patient's own oocytes (Schoolcraft and Gardner, 2000) or equal to them when frozen oocytes or embryos are used (García et al., 2011; Shapiro et al., 2010).

PGS, whether the techniques applied are FISH or comparative genomic hybridization, has made it clear that even donors young than 35 can have embryo aneuploidy rates in excess of 50% (Reis Soares et al., 2005; Baart et al., 2006; Munne et al., 2006). The high response to stimulation has been suggested as the origin of this abnormal embryo aneuploidy rate, showing that it may be possible to improve the chromosomal quality of the embryos with milder stimulation protocols (Baart et al., 2007; Rubio et al., 2010). However, a recent study using comparative genomic hybridization has shown that aneuploidy was not related to the number of oocytes retrieved and embryos generated (Ata et al., 2012). In the current study, in which donors underwent a less intense ovarian stimulation, for 28 cases of OD-RIF who underwent PGS, the abnormal embryo rate was 66.6% and the clinical pregnancy per new donation cycle reached 50% (**Table 2**).

The screening for hereditary or acquired thrombophilia in the population of patients with OD-RIF is a matter of controversy. It is accepted that both recurrent miscarriage and repeated implantation failure may be different manifestations of a common pathological situation in which the fibrinolytic system must clearly be involved (Martinez-Zamora et al., 2011). In the current series, after the usual screening for inherited or acquired thrombophilia in a sample of 131 patients with OD-RIF, abnormal results were found in 16% of the patients. In view of the usual tendency to empirically administer small doses of aspirin to these patients, it is better to carry out a simple selective screening for inherited or acquired thrombophilia that would allow the identification of cases that could benefit from an additional treatment with aspirin or heparin. In the near future, this study centre will have at its disposal biomarkers that will be of assistance in diagnosing these cases.

In conclusion, this study clarifies the criteria for defining what is understood by repeated implantation failure in oocyte donation and suggests that the diagnostic protocol should be widened before new attempts are undertaken. A rigorous andrological study, an endoscopic assessment of the uterine cavity and a screening for thrombophilia may be sufficient to discover pathologies that would otherwise have passed unnoticed. Apart from the therapeutic alternatives that have been proposed, other possibilities should be considered, such as double donation of oocytes and spermatozoa or embryo donation, which might turn out to be a good solution for these patients (Keenan et al., 2012). There has also been a proposal for the intrauterine or systemic administration of HCG or GnRH agonists (Mansour et al., 2011; Tesarik et al., 2004), and there is uterine surrogacy as the final option. However, these clinical observations should be reproduced in other studies and, for the time being, the first strategy should be to complete the diagnosis of OD-RIF and correct any anomalies found before starting a new cycle of oocyte donation.

References

Ata, B., Kaplan, B., Danzer, H., Glassner, M., Opsahl, M., Tan, S.L., Munne, S., 2012. Array CGH análisis shows that aneuploidy is not related to the lumber of embryos generated. Reprod. Biomed. Online 24, 614—620.

Baart, E.B., Martini, E., Van den Berg, I., Macklon, N., Galjaard, R.J., Fauser, B.C., Van Opstal, D., 2006. Preimplantation genetic screening reveals a high incidence of aneuploidy and mosaicism in embryos from young women undergoing IVF. Hum. Reprod. 21—1, 223—233.

Baart, E.B., Martini, E., Eijkemans, M.J., Van Opstal, D., Beckers, N.G., Verhoeff, A., Macklon, N.S., Fauser, B.C., 2007. Milder ovarian stimulation for in vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. Hum. Reprod. 22—4, 980—988.

Bodri, D., Colodron, M., Vidal, R., Galindo, A., Durban, M., Coll, O., 2007. Prognostic factors in oocyte donation: an análisis through egg-sharing recipiente pairs showing a discordante outcome. Fertil. Steril. 88—6, 1548—1553.

Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, 2011. 2009 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Atlanta: U.S. Department of Health and Human Services; 2011. Available from: <http://www.cdc.gov/ART/ART2009>.

Clua, E., Tur, R., Coroleu, B., Boada, M., Barri, P.N., Veiga, A., 2010. Analysis of factors associated with multiple pregnancy in an oocyte donation programme. Reprod. Biomed. Online 21, 694—699.

Das, M., Holzer, H.E.G., 2012. Recurrent implantation failure: gamete and embryo factors. Fertil. Steril. 97—5, 1021—1027.

El-Thouky, T., Sunkara, S., Coomarasamy, A., Grace, J., Khalaf, Y., 2008. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. Reprod. Biomed. Online 16—5, 712—719.

Faddy, M., Gosden, R., Ahuja, K., Elder, K., 2011. Egg sharing for assisted conception: a window on oocyte quality. Reprod. Biomed. Online 22, 88—93.

Ferraretti, A.P., Goossens, V., De Mouzon, J., Bhattacharya, S., Castilla, J.A., Korsak, V., Kupka, M., Nygren, K., NyboeAndersen, A., The European IVF monitoring (EIM) ESHRE Consortium, 2012. Assisted reproductive technology in Europe, 2008: results

generated from European registers by ESHRE. Hum. Reprod. 27, 2571—2584.
García, J.I., Noriega-Portella, L., Noriega-Hoces, L., 2011. Efficacy of oocyte vitrification combined with blastocyst stage transfer in an egg donation program. Hum. Reprod. 26—4, 782—790.
Garrido, N., Bellver, J., Remohi, J., Simon, C., Pellicer, A., 2011. Cumulative live-birth rates per total lumber of embryos needed to reach newborn in consecutive in vitro fertilization (IVF) cycles: a new approach to measuring the likelihood of IVF success. Fertil. Steril. 96—1, 40—46.
Garrido, N., Bellver, J., Remohi, J., Alama, P., Pellicer, A., 2012. Cumulative newborn rates increase with the total number of transferred embryos according to an analysis of 15,792 ovum donation cycles. Fertil. Steril. 98—2, 341—346.
Julve Simon, R., Julve Diaz, X., Labastida, R., 2012. Anomalias uterinas in Donación de ovocitos. Ed. Momento Médico, pp. 221—232.
Johnston-MacAnanny, E.B., Hartnett, J., Engmann, L.L., Nulsen, J.C., Sanders, M., Benadiva, C.A., 2010. Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. Fertil. Steril. 93—2, 437—441.
Keenan, J.A., Gissler, M., Finger, R., 2012. Assisted reproduction using donated embryos: outcomes from surveillance systems in six countries. Hum. Reprod. 27—3, 747—752.
Mansour, R., Tawab, N., Kamal, O., El-Faissal, Y., Serour, A., Aboulghar, M., Serour, G., 2011. Intrauterine injection of human chorionic gonadotropina before embryo transfer significantly improves the implantation and pregnancy rates in in vitro fertilization/intracytoplasmic sperm injection, a prospective randomized study. Fertil. Steril. 96—6, 1370—1374.
Martinez, F., Clua, E., Parera, N., Rodriguez, I., Boada, M., Coroleu, B., 2008. Prospective randomized comparative study of leuprorelin acetate + HMG versus ganirelix + rec FSH in oocyte donors and pregnancy rates amongst the correspondent recipients. Gynecol. Endocrinol. 24—4, 188—193.
Martinez, F., Boada, M., Coroleu, B., Clua, E., Parera, N., Rodriguez, I., Barri, P.N., 2006. A prospective trial comparing oocyte donor ovarian response and recipient pregnancy rates between suppression with GnRH agonist alone and dual suppression with acontraceptive ring and GnRH agonist. Hum. Reprod. 21—8, 2121—2125.
Martinez-Zamora, A., Creus, M., Tassies, D., Reverter, J.C., Civico, S., Carmona, F., Balasch, J., 2011. Reduced plasma fibrinolytic potential in patients with recurrent implantation failure after IVF and embryo transfer. Hum. Reprod. 26—3, 510—516.
Munne, S., Ary, J., Zouves, C., Escudero, T., Barnes, F., Cinioglu, C., Ary, B., Cohen, J., 2006. Wide range of chromosome abnormalities in the embryo of young egg donors. Reprod. Biomed. Online 12—3, 340—346.
Patrizio, P., Sakkas, D., 2009. From oocyte to baby: a clinical evaluation of the biological efficiency of in Vitro fertilization. Fertil. Steril. 91—4, 1061—1066.
Patrizio, P., Bianchi, V., Laliotti, M.D., Gerasimova, T., Sakkas, D., 2006. High rate of biological loss in assisted reproduction: it is in the seed, not in the soil. Reprod. Biomed. Online 14—1, 92—95.
Penzias, A.S., 2012. Recurrent IVF failure: other factors. Fertil. Steril. 97—5, 1033—1038.
Prados, F., Fernandez-Shaw, S., De los Santos, M.J., Cabello, Y., Buxaderas, R., Segura, A., Hernández, J., Vidal, E., Herrero, J., Luceño, F., Marqueta, J., Perez Milan, F., Castilla, J.A., 2011. Registro de la Sociedad Española de Fertilidad: Técnicas de reproducción asistida (IA y FIV/ICSI). Año 2009. Revista Iberoamericana de Fertilidad y Reproducción Humana, vol. 28, Suplemento n 1 Noviembre 2011, pp. 11—46.
Reis Soares, S., Rubio, C., Rodrigo, L., Simon, C., Remohi, J., Pellicer, A., 2003. High frequency of chromosomal abnormalities in embryos obtained from oocyte donation cycles. Fertil. Steril. 80—3, 656—657.
Reis Soares, S., Troncoso, C., Bosch, E., Serra, V., Simon, C., Remohi, J., Pellicer, A., 2005. Age and uterine receptiveness: predicting the outcome of oocyte donation cycles. J. Clin. Endocrinol. Metab. 90—7, 4399—4404.
Rienzi, L., Cobo, A., Paffoni, A., Scarduelli, C., Capalbo, A., Vajta, G., Remohi, J., Ragni, G., Ubaldi, F.M., 2012. Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentric study. Hum. Reprod. 27—6, 1606—1612.
Rubio, C., Mercader, A., Alamá, P., Lizán, C., Rodrigo, L., Labarta, E., Melo, M., Pellicer, A., Remohi, J., 2010. Prospective cohorte study in high responder oocyte donors using two hormonal stimulation protocols: impact on embryo aneuploidy and development. Hum. Reprod. 25—9, 2290—2297.
Ryan Martin, J., Bromer, J.G., Sakkas, D., Patrizio, P., 2010. Live babies born per oocyte retrieved in a subpopulation of oocyte donors with repetitive reproductive success. Fertil. Steril. 94—6, 2064—2068.
Schoolcraft, W.B., Gardner, D.K., 2000. Blastocyst culture and transfer increases the efficiency of oocyte donation. Fertil. Steril. 74—3, 482—486.
Shapiro, B.S., Daneshmand, S.T., Garner, F.C., Aguirre, M., Hudson, C., Thomas, S., 2010. Similar ongoing pregnancy rates after blastocyst transfer in fresh donor cycles and autologous cycles using cryopreserved bipronuclear oocytes suggest similar viability of transferred blastocyst. Fertil. Steril. 93—1, 319—321.
Shariff, K.W., Ghunaim, S., 2010. Management of 273 cases of recurrent implantation failure: results of a combined evidence-based protocol. Reprod. Biomed. Online 21, 373—380.
Simon, A., Laufer, N., 2012. Repeated implantation failure: clinical approach. Fertil. Steril. 97—5, 1039—1043.
Sunkara, S.K., Rittenberg, V., Raine-Fenning, N., Bhattacharya, S., Zamora, J., Coomarasamy, A., 2011. Association between the Lumber of eggs and live Barth in IVF treatment: an análisis of 400, 135 treatment cycles. Hum. Reprod. 26—7, 1768—1774.
Tesarik, J., Hazout, A., Mendoza, C., 2004. Enhancement of embryo developmental potential by a single administration of GnRH agonist at the time of implantation. Hum. Reprod. 19—5, 611—615.
Veiga, A., Calderon, G., Barri, P.N., Coroleu, B., 1987. Pregnancy after the replacement of a frozen-thawed embryo with less than 50% intact blastomeres. Hum. Reprod. 2, 321—323.

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